UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/074,250 | 02/14/2002 | Laura E. Niklason | 1579-637 | 5073 |

23117 7590 01/28/2008

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

| EXAMINER | |
|---|---|
| CHONG, YONG SOO | |
| **ART UNIT** | **PAPER NUMBER** |
| 1617 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 01/28/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/074,250 | NIKLASON ET AL. | |
| | Examiner | Art Unit | |
| | Yong S. Chong | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-23 and 28* is/are pending in the application.

4a) Of the above claim(s) *2-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

In view of the Board Decision filed on 10/18/2007, PROSECUTION IS HEREBY REOPENED. Guidelines are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

Claims 24-27 have been cancelled. Claims 1-23 and 28 are pending.

In view of the Board Decision filed on 10/18/2007, claims 1 (in part), 10, 11 (in part) are allowable as it reads on the elected species, methotrexate.

Examiner will now expand the search to another species, nitric oxide, as recited in claim 28. Therefore, claims 1 and 28 will now be examined herein. Accordingly, claims 2-23, drawn to other patentably distinct species, are withdrawn. The following new rejections will now apply.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for the method of treating progression of cerebral vasospasm that follows subarachnoid hemorrhage, does not reasonably provide enablement for *preventing*. The specification does not enable any person skilled in the art to which it pertains to practice the invention commensurate in scope with these claims. It is noted that Examiner views the term "inhibiting" in claim 1 as "preventing" as it related to the instant invention.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the breadth of the claims; (4) the amount of direction or guidance presented; (5) the predictability or unpredictability of the art; (6) the relative skill of those in the art; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention: The rejected claims are drawn to an invention which pertains to a method of treating and preventing the progression of cerebral vasospasm that follows subarachnoid hemorrhage.

(2) State of the Prior Art: The state of the art regarding treating the progression of cerebral vasospasm that follows subarachnoid hemorrhage is relatively high, however the state of the art for the prevention of the progression of cerebral vasospasm that follows subarachnoid hemorrhage is non-existent.

(3) Breadth of Claims: The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass the prevention, inhibition, and treatment of the progression of cerebral vasospasm that follows subarachnoid hemorrhage.

(4) Guidance of the Specification: The guidance of the specification as to the prevention of the progression of cerebral vasospasm that follows subarachnoid hemorrhage is completely lacking. The specification discloses preventing the onset of the progression of cerebral vasospasm that follows subarachnoid hemorrhage. However, the specification fails to mention how one is able to determine whether the onset of the progression of cerebral vasospasm that follows subarachnoid hemorrhage in a subject would have occurred in the absence of treatment, thus being unable to confirm that prevention has indeed taken place. Moreover, the specification fails to mention the complete prevention or cessation of the progression of cerebral vasospasm that follows subarachnoid hemorrhage once the onset of preclinically evident stage is determined.

(5) The Predictability or Unpredictability of the Art: The invention is directed to a method of treating, inhibiting, and preventing the progression of cerebral vasospasm that follows subarachnoid hemorrhage. The specification does not disclose how one of ordinary skill in the art at the time of the invention would be able to prevent the progression of cerebral vasospasm that follows subarachnoid hemorrhage, nor does the prior art reveal any type of prevention associated with the progression of cerebral vasospasm that follows subarachnoid hemorrhage.

(6) The Relative Skill of those in the Art: One of ordinary skill in the art does not know how to prevent the progression of cerebral vasospasm that follows subarachnoid hemorrhage. Moreover, one is unable to determine whether a subject will ever develop a cerebral vasospasm that follows subarachnoid hemorrhage should this subject be administered nitric oxide.

(7) Working Examples: The specification does not give any data for the prevention of the progression of cerebral vasospasm that follows subarachnoid hemorrhage.

(8) The Quantity of Experimentation Necessary: The specification fails to provide support for the prevention of the progression of cerebral vasospasm that follows subarachnoid hemorrhage. Nor does it provide information to practice the claimed invention, absent undue experimentation. Genetech, 108 F. 3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the progression of cerebral vasospasm that follows subarachnoid hemorrhage by administering nitric oxide, does not reasonably provide enablement for all agents that inhibit vascular cell proliferation sufficient to effect said treatment or inhibition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the breadth of the claims; (4) the amount of direction or guidance presented; (5) the predictability or unpredictability of the art; (6) the relative skill of those in the art; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention: The rejected claims are drawn to an invention which pertains to a method of treating or inhibiting the progression of cerebral vasospasm that follows subarachnoid hemorrhage by administering an agent that inhibits vascular cell proliferation sufficient to effect said treatment or inhibition.

(2) State of the Prior Art: The state of the art regarding treating the progression of cerebral vasospasm that follows subarachnoid hemorrhage is high, however the state of the art regarding agents that inhibit vascular cell proliferation is low.

(3) Breadth of Claims: The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass every agent that inhibits vascular cell proliferation sufficient to affect cerebral vasospasm that follows subarachnoid hemorrhage in a patient.

(4) Guidance of the Specification: The guidance of the specification as to how one of ordinary skill in the art is able to identify an agent that inhibits vascular cell proliferation sufficient to affect cerebral vasospasm that follows subarachnoid hemorrhage in a patient is completely lacking.

(5) The Predictability or Unpredictability of the Art: The invention is directed to every agent that inhibits vascular cell proliferation sufficient to affect cerebral vasospasm that follows subarachnoid hemorrhage in a patient, therefore it is highly unpredictable to identify these agents, let alone determine if these agents are able to treat cerebral vasospasm that follows subarachnoid hemorrhage in a patient

(6) The Relative Skill of those in the Art: One of ordinary skill in the art does not know how to identify an agent that inhibits vascular cell proliferation sufficient to affect

cerebral vasospasm that follows subarachnoid hemorrhage in a patient, let alone determine if these agents are able to treat cerebral vasospasm that follows subarachnoid hemorrhage.

(7) Working Examples: The specification is limiting to the agents listed in the instant claims as it relates to the method of treating or inhibiting the progression of cerebral vasospasm that follows subarachnoid hemorrhage.

(8) The Quantity of Experimentation Necessary: The specification fails to provide support for the method of treating or inhibiting the progression of cerebral vasospasm that follows subarachnoid hemorrhage by administering any and all agents that inhibit vascular cell proliferation sufficient to effect said treatment or inhibition. Nor does it provide information to practice the claimed invention, absent undue experimentation. Genetech, 108 F. 3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The structure is critical or essential to the practice of

the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The elected compound in claim 1 is defined only by their function and not by their structure. Claim 1 uses any compound, which "inhibits vascular cell proliferation." This requires the use of an undefined, unsupported class of compounds in the method. The dependent claims lists certain compounds falling within the scope of the claim, however there is no overall common core or structure to these compounds which would lead one of ordinary skill in the art to the full scope of the claims. As the claims encompass an agent that inhibits vascular cell proliferation, there is no correlation between the structure and function for the compounds to be used in this method. There does not appear to be an art recognized definition of a class of compounds or compositions that carry out the aforementioned function.

The following logic is from the Trilateral agreement on reach-through claims: "The claims encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would

fall within the scope of what is claimed. It would require undue experimentation (be undue burden) to randomly screen undefined compounds for the claimed activity."

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation "an agent that inhibits vascular cell proliferation sufficient to effect said treatment or inhibition" renders the claim indefinite as to what exactly this agent is. The specification does not clearly disclose or teach how one is able to determine or identify an agent that inhibits vascular cell proliferation sufficient to effect said treatment or inhibition. Therefore, the metes and bounds of patent protection sought for this specific limitation has not been defined.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Sackner et al. (US Patent Application 2002/0103454 A1).

Sackner et al. teach treating cerebral vasospasm after subarachnoid hemorrhage by administering nitroglycerin transdermally (section 0261). It is noted that Sackner et al. discloses that nitroglycerin releases nitric oxide through enzymatic degradation (section 0018). Sackner et al. also teach that external additions of pulses to the circulation by releasing nitric oxide from vascular endothelium relieves cerebral vasospasm associated with subarachnoid hemorrhage (section 0262).

Claims 1 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Tedeschi et al. (US Patent 6,379,691 B1).

Tedeschi et al. teach the benefits of nitric oxide therapy in the reversal of cerebral vasospasms (col. 6, lines 18-44). It is noted that cerebral vasospasm is associated with subarachnoid hemorrhage (pg. 1, top right column).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being obvious over Keefer (US Patent 4,954,526) in view of Harder et al. (US Patent 4,792,564).

The instant claims are directed to a method of treating the progression of cerebral vasospasm that follows subarachnoid hemorrhage comprising administering to a patient in need thereof nitric oxide.

Keefer teaches the treatment of cerebral vasospasm by administering a compound of formula I, which are stable nitric oxide primary amine complexes that release nitric oxide in vivo in a controlled fashion (col. 3, lines 24-32).

However, Keefer fail to disclose specifically a patient population having cerebral vasospasm after subarachnoid hemorrhage.

Harder et al. teach that cerebral vasospasm usually follows subarachnoid hemorrhage and that cerebral vasospasm is the leading cause of death in cases of subarachnoid hemorrhage (col. 1, lines 6-13).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have administered nitric oxide in

a patient suffering from cerebral vasospasm after having suffered subarachnoid hemorrhage.

A person of ordinary skill in the art would have been motivated to have administered nitric oxide in a patient suffering from cerebral vasospasm after having suffered subarachnoid hemorrhage because: (1) Keefer teaches the treatment of cerebral vasospasm by administering nitric oxide; (2) Harder et al. teaches that cerebral vasospasm usually follows subarachnoid hemorrhage; and (3) Harder et al. teaches that cerebral vasospasm is the leading cause of death in cases of subarachnoid hemorrhage. Therefore, the skilled artisan would have had a reasonable expectation of success in similarly treating a patient suffering from cerebral vasospasm after having suffered subarachnoid hemorrhage as compared to treating a patient suffering from cerebral vasospasm by administering nitric oxide.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC